CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074813

Trade Name : ETOPOSIDE INJECTION 20MG/ML

Generic Name: Etoposide Injection 20mg/ml, 5ml multiple dose vials

Sponsor : Guidelines, Inc.

Approval Date: July 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074813

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Correspondence				

ANDA 74-813

JUL 9 1997

Guidelines, Inc.
U. S. Agent for Pierre Fabre Medicament
Attention: David M. Cohen, Ph.D.
10320 USA Today Way
Miramar Park of Commerce
Miramar, Floria 33025

Dear Sir:

This is in reference to your abbreviated new drug application dated December 21, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etoposide Injection, 20 mg/mL (5 mL Multiple Dose Vials).

Reference is also made to your amendments dated October 21, 1996; and April 17, and June 13, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etoposide Injection, 20 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to that of the listed drug (VePesid® Injection, 20 mg/mL, of Bristol Laboratories, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

/S/ 7/8/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074813

FINAL PRINTED LABELING

9 1997

PIERRE FABRE MEDICAMENT

ETOPOSIDE INJECTION

WARNINGS

Etoposide should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

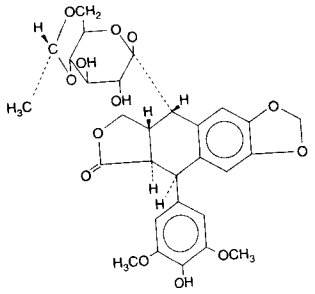
DESCRIPTION

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4' - demethylepipodophyllotoxin 9-[4,6-0-(R)-ethylidene-ß-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.56 and a molecular formula of $C_{29}H_{32}O_{13}$.

Etoposide Injection is available for intravenous use as a sterile 20 mg/mL solution in 5 mL multiple dose vials.

The pH of the clear yellow solution is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.

The structural formula is:



CLINICAL PHARMACOLOGY

Etoposide has been shown to cause metaphase arrest in chick fibroblasts. Its main effect, however, appears to be at the G_2 portion of the cell cycle in mammalian cells.

Two different dose-dependent responses are seen. At high concentrations (10 mcg/mL or more), lysis of cells entering mitosis is observed. At low concentrations (0.3 to 10 mcg/mL), cells are inhibited from entering prophase. It does not interfere with microtubular assembly. The predominant macromolecular effect of etoposide appears to be DNA synthesis inhibition.

Pharmacokinetics: On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours. Today body clearance values range from 33 to 48 mL/min or 16 to 36 mL/min/m^2 and, like the terminal elimination half-life, are independent of dose over a range 100-600 mg/m^2. Over the same dose range, the areas under the plasma concentration vs time curves (AUC) and the maximum plasma concentration (Cmax) values increase linearly with dose. Etoposide does not accumulate in the plasma following daily administration of 100 mg/m^2 for 4 to 5 days.

The mean volumes of distribution at steady state fall in the range of 18 to 29 liters or 7 to 17 L/m^2. Etoposide enters the CSF poorly. Although it is detectable in CSF and intracerebral tumors, the concentrations are lower than in extracerebral tumors and in plasma. Etoposide concentrations are higher in normal lung than in lung metastases and are similar in primary tumors and normal tissues of the myometrium. *In vitro*, etoposide is highly protein bound (97%) to human plasma proteins. An inverse relationship between plasma albumin levels and etoposide renal clearance is found in children. In a study determining the effect of other therapeutic agents on the *in vitro* binding of carbon-14 labeled etoposide to human serum proteins, only phenylbutazone, sodium salicylate, and aspirin displaced protein-bound etoposide at concentrations achieved *in vivo*.[1]

Etoposide binding ratio correlates directly with serum albumin in patients with cancer and in normal volunteers. The unbound fraction of etoposide significantly correlated with bilirubin in a population of cancer patients.[2,3]

After intravenous administration of ^{3}H-etoposide (70-290 mg/m^2), mean recoveries of radioactivity in the urine range from 42 to 67%, and fecal recoveries range from 0 to 16% of the dose. Less than 50% of an intravenous dose is excreted in the urine as etoposide with mean recoveries of 8 to 35% within 24 hours.

In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m^2 or about 35% of the total body clearance over a dose range of 80 to 600 mg/m^2. Etoposide, therefore, is cleared by both renal and nonrenal processes, ie, metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known.

Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the nonrenal clearance of etoposide. The major urinary metabolite of etoposide in adults and children is the hydroxy acid [4'-demethylepipodophyllic acid-9-(4,6-0-(R)-ethylidene-ß-D-glucopyranoside)], formed by opening of the lactone ring. It is also present in human plasma, presumably as the trans isomer. Glucuronide and/or sulfate conjugates of etoposide are excreted in human urine and represent 5 to 22% of the dose.

After either intravenous infusion or oral capsule administration, the Cmax and AUC values exhibit marked intra- and inter-subject variability.

In adults, the total body clearance of etoposide is correlated with creatinine clearance, serum albumin concentration, and nonrenal clearance. In children, elevated serum SGPT levels are associated with reduced drug total body clearance. Prior use of cisplatin may also result in a decrease of etoposide total body clearance in children.

INDICATIONS AND USAGE

Etoposide Injection is indicated in the management of the following neoplasms:

Refractory Testicular Tumors - Etoposide Injection in combination therapy with other approved chemotherapeutic agents in patients with refractory testicular tumors who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy.

Small Cell Lung Cancer - Etoposide Injection and/or Capsules in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer.

CONTRAINDICATIONS

Etoposide Injection is contraindicated in patients who have demonstrated a previous hypersensitivity to etoposide or any component of the formulation.

WARNINGS

Patients being treated with etoposide must be frequently observed for myelosuppression both during and after therapy. Dose-limiting bone marrow suppression is the most significant toxicity associated with Etoposide therapy. Therefore, the following studies should be obtained at the start of the therapy and prior to each subsequent dose of etoposide: platelet count, hemoglobin, white blood cell count, and differential. The occurrence of a platelet count below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered.

Physicians should be aware of the possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. (See "ADVERSE REACTIONS" section.) Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician.

Etoposide Injection should be given only by slow Intravenous Infusion (usually over a 30 to 60 minute period) since hypotension has been reported as a possible side effect of rapid intravenous injection.

Pregnancy: Pregnancy "Category D". Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Etoposide is teratogenic and embryocidal in rats and mice at doses of 1 to 3% of the recommended clinical dose based on body surface area.

In a teratology study in SPF rats, etoposide was administered intravenously at doses of 0.13, 0.4, 1.2 and 3.6 mg/kg/day on days 6 to 15 of gestation. Etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity at dose levels of 0.4 mg/kg/day and higher. Embryonic resorptions were 90 and 100% at the 2 highest dosages. At 0.4 and 1.2 mg/kg, fetal weights were decreased and fetal abnormalities including decreased weight, major skeletal abnormalities, exencephaly, encephalocele and anophthalmia occurred. Even at the lowest dose tested 0.13 mg/kg, a significant increase in retarded ossification was observed.

Etoposide Injection administered as a single intraperitoneal injection in Swiss-Albino mice at dosages of 1, 1.5 and 2 mg/kg on days 6, 7 or 8 of gestation caused dose-related embryotoxicity, cranial abnormalities, and major skeletal malformations.

PRECAUTIONS

General: In all instances where the use of etoposide is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse reactions. Most such adverse reactions are reversible if detected early. If severe reactions occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of etoposide therapy should be carried out with caution, and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

Laboratory Tests: Periodic complete blood counts should be done during the course of etoposide treatment. They should be performed prior to therapy and at appropriate intervals during and after therapy. At least one determination should be done prior to each dose of etoposide.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity tests with etoposide have not been conducted in laboratory animals. Etoposide should be considered a potential carcinogen in humans. The occurence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

The mutagenic and genotoxic potential of etoposide has been established in mammalian cells. Etoposide caused aberrations in chromosome number and structure in embryonic murine cells and human hematopoletic cells: gene mutations in Chinese hamster ovary cells, and DNA damage by strand breakage and DNA-protein cross-links in mouse leukemia cells. Etoposide also caused a dose-related increase in sister chromatid exchanges in Chinese hamster ovary cells.

Treatment of Swiss-Albino mice with 1.5 mg/kg IP of etoposide on day 7 of gestation increased the incidence of intrauterine death and fetal malformations as well as significantly decreased the average fetal body weight. Maternal weight gain was not affected.

Treatment of pregnant SPF rats with 1.2 mg/kg/day IV of etoposide for 10 days led to a prenatal mortality of 92% and 50% of the implanting fetuses were abnormal.

Pregnancy: Teratogenic Effects - Pregnancy Category D. (See "WARNINGS" section.)

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etoposide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Etoposide Injection contains polysorbate 80. In premature infants, a life-threatening syndrome consisting of liver and renal failure, pulmonary deterioration, thrombocytopenia, and ascites has been associated with an injectable vitamin E product containing polysorbate 80.

ADVERSE REACTIONS

The following data on adverse reactions are based on both oral and intravenous administration of etoposide as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic Toxicity: Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with etoposide in association with other antineoplastic agents.

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that etoposide be administered by slow intravenous infusion over a 30 to 60 minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous etoposide and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of etoposide.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness, was observed in up to 66% of patients.

Other Toxicities: The following adverse reactions have been infrequently reported: aftertaste, fever, pigmentation, abdominal pain, constipation, dysphagia, transient cortical blindness, optic neuritis, and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with etoposide. Metabolic acidosis has also been reported in patients receiving higher doses.

The incidences of adverse reactions in the table that follows are derived from multiple data bases from studies in 2,081 patients when etoposide was used either orally or by injection as a single agent.

Adverse drug effect	Percent range of reported incidence
Hematologic Toxicity	
Leukopenia (less than 1,000 WBC/mm^3	3-17
Leukopenia (less than 4,000 WBC/mm^3	60-91
Thrombocytopenia (less than 50,000 platelets/mm^3	1-20
Thrombocytopenia (less than 100,000 platelets/mm^3	22-41
Anemia	0-33
Gastrointestinal Toxicity	
Nausea and vomiting	31-43
Abdominal pain	0-2
Anorexia	10-13
Diarrhea	1-13
Stomatitis	1-6
Hepatic	0-3
Alopecia	8-66
Peripheral Neurotoxicity	1-2
Hypotension	1-2
Allergic Reaction	1-2

OVERDOSAGE

No proven antidotes have been established for etoposide overdosage.

DOSAGE AND ADMINISTRATION

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with *undiluted* Etoposide Injection.

Etoposide Injection: The usual dose of Etoposide Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m^2/day on days 1 through 5 to 100 mg/m^2/day on days 1, 3 and 5.

In small cell lung cancer, the Etoposide Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days.

Chemotherapy courses are repeated at 3 to 4 week intervals after adequate recovery from any toxicity.

Dosage should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration Precautions: As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of etoposide. Skin reactions associated with accidental exposure to etoposide may occur. The use of gloves is recommended. If etoposide solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Preparation for intravenous Administration: Etoposide Injection must be diluted prior to use with either 5% Dextrose injection or 0.9% Sodium Chloride injection to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the etoposide solution be administrated over a 30 to 60 minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. **Etoposide should not be given by rapid intravenous injection.**

Parenteral drug products should be inspected visually for particulate matter and discoloration (see "DESCRIPTION" section) prior to administration whenever solution and container permit.

Stability: Unopened vials of Etoposide Injection are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 to 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published [4-10]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Etoposide Injection 20 mg/mL is supplied as follows:

NDC (applied for) - 100 mg/5mL, Multiple Dose Vials.

Store at controlled room temperature 15° to 30°C (59° to 86° F).

CAUTION : Federal (USA) law prohibits dispensing without prescripition.

References:

1. Gaver RC; Deeb G; "The effect of other drugs on the *in vitro* binding of 14C-etoposide to human serum proteins." Proc Am Assoc Cancer Res; 30:A2132, 1989.
2. Stewart CF; Pieper JA; Arbuck SG; Evans WE; "Altered protein binding of etoposide in patients with cancer" Clin Pharmacol Ther; 45:49-55, 1989.
3. Stewart CF; Arbuck SG; Fleming RA; Evans WE; "Prospective evaluation of a model for predicting etoposide plasma protein binding in cancer patients." Proc Am Assoc Cancer Res; 30:A958, 1989.
4. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Wahshington, D.C. 20402.
5. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253(11):1590-1592.
6. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
7. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.
8. Jones RB, et al; Safe handling of chemotherapeutic agents: A report from the Mount Sinal Medial Center. CA-A Cancer Journal for Clinicians 1983; (Sept/Oct) 258-263.
9. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm 1990; 47:1033-1049.
10. OSHA Work-Practice Guidelines for Personnel. Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm 1986; 43:1193-1204.

Revised March 1997

PIERRE FABRE MEDICAMENT
45, place Abel-Gance
92654 BOULOGNE Cedex
FRANCE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074813

CHEMISTRY REVIEW(S)

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: Addendum #1 to CR #2
(Note: chem. closed after CR #2).

2. **ANDA**: 74-813

3. **NAME AND ADDRESS OF APPLICANT**:
Pierre Fabre Medicament
Pierre Fabre Medicament
Attention: Didier Caizergues
(Head of International Regulatory Affairs)
45 Place Abel Gance
92654 Boulogne Cedex, France
Phone: 011-33-1-49-10-8000

US Agent:
David M. Cohen, Ph.D.
Guidelines, Inc.
10320 USA Today Way, Miramar Park of Commerce
Miramar, Florida 33025
Phone: (954) 433-7480; Fax (954) 432-9015

4. **LEGAL BASIS FOR ANDA SUBMISSION**: See CR #1 for details.

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**: Etoposide Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
* denotes the document(s) being reviewed in this review.
Pierre Fabre:

12/21/95	ANDA submission (received on 12/26/95)
03/06/96	Amendment (response to refuse to File)
10/21/96	Response to NA (MAJOR) letter of 07/12/96
04/17/97	Labeling Amendment
06/13/97*	Telephone amendment (Re: Method Validation)

FDA:

02/02/96	Refuse to File letter
03/18/96	Acknowledge of submission. (date acceptable for filing: 03/07/96)
06/27/96	Bio acceptance letter
07/12/96	NA (MAJOR) letter (from CR #1 by Liu & Labeling review by Holquist)
06/10/97	Request a telephone amendment(Re: Method Valid).

10. **PHARMACOLOGIC CATEGORY**: Antineoplastic

11. **HOW DISPENSED**: Rx

12. **RELATED INDs, NDAs and DMFs**: See CR #1

13. **DOSAGE FORM**:
Parenteral (intravenous)

14. **STRENGTH**:
20 mg/mL (100 mg/vial)

15. **CHEMICAL STRUCTURE AND NAME**: See CR #1.

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
The new Office policy prompted Branch II to contact the firm's US Agent to request a telephone amendment. As per Agency's request, the applicant provided a formal commitment dated June 13, 1997, signed by Didier Caizergues (Head of International Regulatory Affairs of Pierre Fabre Medicament) to expeditiously resolve any issues that may arise from the completion of the method validation work that is still pending for the drug product. Additionally, the new labeling amendment has been reviewed by Carol Holquist and found acceptable.

18. **CONCLUSIONS/RECOMMENDATIONS**:
The commitment is acceptable. Since labeling, bio, micro, EER, chem, method validation commitment are all satisfactory, the application is approvable. An approval package will be prepared.

19. **REVIEWER**:
Shing H. Liu, Ph.D.

DATE COMPLETED/REVISED:
Completed 06/17/97

cc:
ANDA 74-813
DUP JACKET
Division File
FIELD COPY

Endorsements:
HFD-625/SLiu/06/17/97 /S/ 06/23/97
HFD-625/MSmela/06/18/97 6/23/97
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F/T by: gp/06/20/97

Chemistry Closed

Office of Generic Drugs

Chemistry, Manufacturing and Controls Review

1. **REVIEW NUMBER**: No. 2

2. **ANDA**: 74-813

3. **NAME AND ADDRESS OF APPLICANT**:

Pierre Fabre Medicament
Attention: Didier Caizergues
(Head of International Regulatory Affairs)
45 Place Abel Gance
92654 Boulogne Cedex, France
Phone: 011-33-1-49-10-8000

US Agent:
David M. Cohen, Ph.D.
Guidelines, Inc.
10320 USA Today Way, Miramar Park of Commerce
Miramar, Florida 33025
Phone: (954) 433-7480; Fax (954) 432-9015

4. **LEGAL BASIS FOR ANDA SUBMISSION**:
See CR #1 for details.

5. **SUPPLEMENT(S)**: N/A 6. **DRUG NAME**: N/A

7. **NONPROPRIETARY NAME**: Etoposide Injection

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
* denotes the document(s) being reviewed in this review.

Pierre Fabre:

12/21/95	ANDA submission (received on 12/26/95)
03/06/96	Amendment (response to refuse to File)
10/21/96*	Response to NA (MAJOR) letter of 07/12/96

FDA:

02/02/96	Refuse to File letter
03/18/96	Acknowledge of submission. (date acceptable for filing: 03/07/96)
06/27/96	Bio acceptance letter
07/12/96	NA (MAJOR) letter (from CR #1 by Liu & Labeling review by Holquist)

10. **PHARMACOLOGIC CATEGORY**: Antineoplastic

11. **HOW DISPENSED**: Rx

12. **RELATED INDs, NDAs and DMFs:** See CR #1

13. **DOSAGE FORM:**
Parenteral (intravenous)

14. **STRENGTH:**
20 mg/mL (100 mg/vial)

15. **CHEMICAL STRUCTURE AND NAME:** See CR #1.

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
The drug substance has a USP monograph. The drug product is not a subject of the USP 23 (up to Supplement 5).

Pierrte Fabre Medicament (PF) is a privately owned French pharmaceutical company.

PF's response to chemistry and microbiological deficiencies are acceptable. Bioequivalence waiver request has been granted. There are still labeling deficiencies.

Since control related issues are now resolved, the method validation request is to be issued.

18. **CONCLUSIONS/RECOMMENDATIONS:**
Chemistry closed. Labeling should issue their comments to PF directly.

19. **REVIEWER:**
Shing H. Liu, Ph.D.

DATE COMPLETED/REVISED:
Completed 03/18/97
Updated 03/24/97

cc: ANDA 74-813
DUP JACKET
Division File
FIELD COPY

Endorsements:
HFD-625/SLiu/03/18/97/03/24/97 /S/ 3/24/97
HFD-625/MSmela/
x:\new\firmsnz\pierrefa\ltrs&rev\74813CR2.MAJ
F/T by: /S/ 3/24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074813

BIOEQUIVALENCE REVIEW(S)

JUN 27 1996

ANDA 74-813

Guidelines, Inc.
U.S. Agent for: Pierre Fabre Medicament
Attention: David M. Cohen, Ph.D.
10320 USA Today Way
Miramar, Fl 33025

Dear Dr. Cohen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etoposide Injection, 20 mg/mL (5 mL MDV).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 20 1996

Etoposide Injection, 20 mg/mL
5 mL Multiple Dose Vial,
100 mg/Vial
ANDA #74-813
Reviewer: Moheb H. Makary
WP. 74813W.D95

Pierre Fabre Medicament
Boulogone Cedex, France
Submission Date:
December 21, 1995

Review a Request for Waiver

I. Objective:

The firm requested waiver of bioequivalence study requirements for its product Etoposide Injection, 20 mg/mL, 5 mL Multiple Dose Vial, 100 mg/vial. Innovator product is VePesid® Injection 20 mg/mL, manufactured by Bristol-Myers Squibb.

Etoposide is indicated for the management of refractory testicular tumors and small cell lung cancer.

II. Formulations:

The formulations of the proposed test product and reference product are shown below:

Ingredients	Proposed Test Product Etoposide Injection Pierre Fabre Medicament	Reference Product VePesid® Injection Bristol-Myers Squibb
Etoposide USP	20 mg/mL	20 mg/mL
Citric Acid USP	2 mg/mL	2 mg/mL
Benzyl Alcohol NF 18	30 mg/mL	30 mg/mL
Polysorbate 80 NF 18	80 mg/mL	80 mg/mL
Polyethylene glycol 300	650 mg/mL	650 mg/mL
Dehydrated Alcohol USP	30.5% v/v	30.5% v/v
Nitrogen 99.99%	ad libidum	ad libidum

III. Comment:

As shown above, the proposed test product, Etoposid Injection, 20 mg/mL, 5 mL Multiple Dose Vial, 100 mg/Vial contains the same active and inactive ingredients in the same quantities per mL as the reference product, VePesid® Injection, 20 mg/mL, 100 mg/Vial. Waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (b)(1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Pierre Fabre Medicament, demonstrates that Etoposide Injection 20 mg/mL, 5 mL Multiple Dose Vial, 100 mg/Vial, falls under Section 320.22 (b)(1) of Bioavailability/Bioequivalence

Regulations. Waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, Etoposide Injection 20 mg/mL, 5 mL Multiple Dose Vial, 100 mg/Vial, manufactured by Pierre Fabre Medicament, to be bioequivalent to VePesid® Injection 20 mg/mL, 100 mg/5 mL Sterile, Multiple Dose Vial manufactured by Bristol-Myers Squibb.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE Date: 6/18/96

Concur: /S/ Date: 6/20/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/6-17-96 wp 74813W.D95
cc: ANDA #74-813, original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Makary), Drug File, Division File.